

**REMARKS**

Claims 99, 101-103, 105, 107, 108 and 110-121 are pending in the application. All claims have been rejected.

Claims 99, 101, 102, 103, 105, 107, 108, and 110-121 have been rejected under 35 USC 103(a), as being unpatentable over Arad et al. (US Patent No. 5,534,417) or Lee et al. (Biotech. Bioeng), in view of Kalfon (EP Patent No. 343885), or Hitzman (US Patent No. 4,519,984), or Kobayashi (US Patent No. 5,565,051), or Whitney (GB Patent No. 2,202,549). Claims 99-121 have been rejected for obviousness-type double patenting. Claims 99 and 101 have now been amended. No new subject matter has been introduced.

***Double Patenting***

The Examiner has rejected claims 99, 101-103, 105, 107, 108 and 110-121 on the ground of non-statutory obviousness type double patenting as being unpatentable over claims 1-45 of US Patent No. 6,391,638 and over claims 1-45 of US Patent No. 6,391,638 in view of Lee et al (Biotech. Bioeng.).

Issues of obviousness-type double-patenting and the submission of a terminal disclaimer will be further considered with respect to US Patent No. 6,391,638 and Lee et al. upon indication by the Examiner of allowable claims in the present case.

***CLAIM REJECTIONS***

***35 U.S.C. § 103(a) Rejection over Arad et al (US Patent No. 5,534,417) in view of Kalfon (EP Patent No. 343885), or Hitzman (US Patent No. 4,519,984), or Kobayashi (US Patent No. 5,565,051), or Whitney (GB Patent No. 2,202,549) or Lee et al. (Biotech. Bioeng.)***

The Examiner has rejected claims 99, 101, 102, 103, 105, 107, 108, and 110-121 under 35 USC 103(a), as being obvious over Arad et al (US Patent No. 5,534,417), in view of Kalfon (EP Patent No. 343885)(103), or Hitzman (US Patent No. 4,519,984)(99, 101, 102, 105, 108, 110-114 and 116-121), or Kobayashi (US Patent No. 5,565,051)(107), or Whitney (GB Patent No. 2,202,549)(115). Claims 99, 101, 102, 103, 105, 107, 108, and 110-121 have further been rejected under 35 USC 103(a), as being obvious over Arad et al (US Patent No. 5,534,417), in view of Lee et al (Biotech. Bioeng.)(99, 101, 102, 105, 108, 110-114 and 116-121), or Kalfon (EP

Patent No. 343885)(103), or Kobayashi (US Patent No. 5,565,051)(107), or Whitney (GB Patent No. 2,202,549)(115). Claims 99 and 101 have now been amended. The Examiner's rejection is respectfully traversed.

Applicant maintains that the container for growing microalgae, aerated with a gas (air) from a pipe introduced from above, and having a fluid inlet/outlet for filling and emptying as taught by Arad et al. is incompatible with the plant culture bioreactor of the system as claimed, and that none of the cited publications remedy the shortcomings of Arad et al.

In order to expedite prosecution in this case, the system as claimed in amended claim 99 now includes the following limitations:

- 1) At least one disposable device comprising a sterilisable disposable container which comprises
  - a) a reusable harvester which comprises a flow controller; and
  - b) at least two air inlets being positioned at or near the bottom end of said device, and wherein said air inlets are designed to produce bubbles comprising a mean diameter of between 1 and 10 mm;
- 2) wherein the device can be used continuously for at least one further consecutive culturing/harvesting cycle,
- 3) wherein a remainder of medium containing cells and/or tissue, remaining from a previous harvested cycle, may serve as inoculant for a next culture and harvest cycle,
- 4) wherein said cells and/or tissue are plant cells and/or plant tissue,
- 5) further comprising a culture of carrot cells expressing a recombinant human lysosomal protein.

Support for such an amendment is found throughout the instant specification, for example, Example 5 of the Results section, and pages 6 and 9:

According to preferred embodiments of the present invention, the present invention is adapted for use with plant cell culture, for example by providing a low shear force while still maintaining the proper flow of gas and/or liquids, and/or while maintaining the proper mixing conditions within the container of the device of the present invention. For example, optionally and preferably the cells are grown in suspension, and aeration (flow of air through

the medium, although optionally any other gas or gas combination could be used) is performed such that low shear force is present. To assist the maintenance of low shear force, optionally and preferably the container for containing the cell culture is made from a flexible material and is also at least rounded in shape, and is more preferably cylindrical and/or spherical in shape. These characteristics also optionally provide an optional but preferred aspect of the container, which is maintenance of even flow and even shear forces.

It should be noted that the term "plant culture" as used herein includes any type of transgenic and/or otherwise genetically engineered plant cell that is grown in culture. The genetic engineering may optionally be permanent or transient. Preferably, the culture features cells that are not assembled to form a complete plant, such that at least one biological structure of a plant is not present. Optionally and preferably, the culture may feature a plurality of different types of plant cells, but preferably the culture features a particular type of plant cell. It should be noted that optionally plant cultures featuring a particular type of plant cell may be originally derived from a plurality of different types of such plant cells."(page 6, line 7 to page 7, line 17); and

As indicated above, the host cells of the invention may be transfected or transformed with a nucleic acid molecule. As used herein, the term "nucleic acid" refers to polynucleotides such as deoxyribonucleic acid (DNA), and, where appropriate, ribonucleic acid (RNA)...In yet another embodiment, the host cell of the invention may be transfected or transformed with an expression vector comprising the recombinant nucleic acid molecule. (page 9, line 19 to page 10, line 6)

Claim 101 has been amended to further include the limitation of the human recombinant lysosomal protein being human glucocerebrosidase. Support for such an amendment can be found throughout the instant specification, for example, Example 5 of the Results section (see FIGs. 12, 13 and 17-24).

Applicant wishes to point out that it is not at all understood that the container and culture conditions as taught by Arad et al. are suitable for culturing transformed carrot cells expressing a human lysosomal protein. Microalgae, such as the *Dunaliella bardawilli* grown in the container (see Arad et al., Example 2) are motile

bi-flagellated cells approximately 10x6  $\mu\text{m}$  in size enclosed by a thin later of elastic plasma membrane and are characterized by extreme halotolerance (capable of growth in 0.2 to 35% salinity) and rapid volume changes in response to variation in osmotic pressure. Carrot cells in suspension culture, in contrast, are non-motile, approximately 50-100  $\mu\text{m}$  in size, and possess cellulose cell walls with high glucomannin content. Thus, factors governing shear forces, pH and osmotic effects suitable for use in the microalgae culture as taught by Arad et al. cannot be extrapolated to high volume suspension culture of recombinant carrot cells, as in the claimed invention.

Inasmuch as Arad et al. is silent regarding culturing plant cells expressing recombinant proteins, and provides no guidance for the preparation or practice of such recombinant plant cell culture, and Lee et al., Kalfon, Hitzman et al, Kobyashi et al. or Whitney et al. all fail to teach such a limitation, Applicant submits that Arad et al., alone or in combination with other cited references cannot render obvious the claimed recombinant plant cell culture system.

Applicant respectfully requests withdrawal of the 103(a) rejections.

In view of the foregoing amendments and remarks, pending claim 99 and claims dependent therefrom are deemed to be allowable. Their favorable reconsideration and allowance is respectfully requested.

Respectfully submitted,



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Date: May 14, 2009

**Enclosures:**

- ☐ Petition for Extension (Three Month)
- ☐ Request for Continued Examination (RCE)